31. The improved method of claim 23, wherein treatment according to the method has at least one of the following effects:

a) substantial regression of the tumor in size;

b) lack of recurrence of a tumor after removal; or

c) decrease in rate of formation of metastasis.

REMARKS

This paper is responsive to the Office Action dated October 3, 2002, which is the fourth non-final action on the merits of the application. Claims 1-22 were pending in this application, and stand variously rejected. By way of this Amendment, claims 15, 17, and 21 are canceled, and claims 23-31 are added. Accordingly, claims 1-14, 16, 18-20, and 22-31 are under examination.

The new claims and claim amendments are supported at various places in the application as filed, and by the claims as previously presented. The new limitation in claim 1 comes from claim 21. The time period recited in new claim 23 (one to eight weeks) comes from claim 7. Accordingly, entry of this Amendment does not introduce new matter into the disclosure.

Reconsideration and allowance of the application in view of the amendments and remarks made in this paper is respectfully requested.

Interview Summary

The undersigned wishes to express his gratitude to Dr. Shin-Lin Chen for the helpful and constructive interview conducted at the Patent Office on September 11, 2002.

This response incorporates the suggestions made by the Examiner at the interview, both in the claim amendments and in the remarks. Applicant has selected for presentation in this Response the claim limitations which the Examiner indicated would be helpful in overcoming the prior art rejections. The amended claims are believed to be in condition for allowance, which is respectfully requested.

The Granger Patent

Claims 1-10, 12-16, and 18-20 remain rejected under 35 USC §§ 102(b) and 103(a) as being anticipated or obvious over U.S. Patent 5,837,233 (the Granger Patent). Claims 11 and 17 stand rejected under 35 USC § 103(a) as being unpatentable over the Granger Patent when combined with secondary references by Feldhaus et al., and Haugland.

Applicants maintain that the claims previously presented are patentable over the Granger Patent for reasons indicated in the last Amendment.

Nevertheless, to advance prosecution of this application, additional limitations have been incorporated into the claims which provide further distinguishing features from what is described and enabled by the Granger Patent.

Applicant is grateful for the indication in the Office Action that previous claims 21 and 22 are not anticipated or obvious with respect to Granger. Claim 1 and its dependents now incorporate the limitation of previous claim 21, and is believed to be in condition for allowance

As explained previously and at the interview, the need to administer multiple sequential implants into a site in a patient containing tumor antigen encourages the clinician to *leave tumor cells behind* at the time of the first injection. This is exactly what was done in Example 6 of the disclosure, where multiple implants were administered to the same tumor. The effect was quite remarkable. Three out of five subjects treated twice with implants from the same donor showed *complete regression* of their tumor (Figure 5), and survived more than twice as long as subjects treated with only a single implant (Figure 4). Furthermore, animals treated with two implants in a metastasis model were found to be completely immune to rechallenge with the same tumor (Table 6). Resistance to rechallenge was tumor-type specific, which is consistent with a vigorous immune-mediated reaction by the host against the primary tumor.

But it is entirely counter-intuitive for a clinician to leave tumor cells in a patient, when the tumor is sufficiently accessible to be removed. A skilled reader of the Granger Patent would remove all of the tumor as a matter of course, which is exactly what was done in the clinical trial that Granger shows in Fig. 1 and Fig. 2. Accordingly, Claim 1 of this application as amended is distinguished over Granger, *inter alia* because it requires leaving tumor cells in the patient between injections, which would not suggest itself to someone skilled in the art reading the Granger patent.

New Claim 23 and its dependents are also not suggested by the Granger patent, because the second implant of alloactivated cells is required to be administered one to eight weeks after the first implant. As explained at the interview, this is before the clinician would normally have an indication as to the effect of the first implant.

The Office reasons that the clinician may decide to administer a second dose of a cancer therapeutic if the first administration was determined to be below an effective amount in the particular patient being treated. Even if this were true for the type of therapeutic taught in the Granger application, this logic requires the clinician to obtain a read-out of the first administration before proceeding — especially for a procedure that can be as invasive and expensive as the implanting of alloactivated cells into a particular site.

Figure 2 of the Granger Patent illustrates the paucity of data that is available within the first eight weeks of the first administration. The graph shows activity at the primary site, measured by magnetic resonance imaging (MRI). The volumes observed are attributable to both inflammation in the cavity after removal of the primary tumor, and potentially, re-establishment of a tumor when the treatment fails. As long as the lines are downward sloping, there is no reason to suspect the initial implant isn't being effective. There is no evidence for upward sloping volumes *in any of the patients treated* until well outside the eight week window. Accordingly, there would be no motivation from such data for a clinician to administer a second implant of alloactivated cells so early in the course of therapy.

In contrast, Claim 23 requires that the second implant be performed *within eight weeks* of the first implant, so the patient can accrue the benefits of the sequential implant strategy as early as possible. The practicing clinician would not know to do this, except through the teachings of this patent application.

Applicant disagrees that there is motivation to combine the Granger Patent with the references by Feldhaus et al. and Haugland, or that the combination affects the patentability of Claims 11 and 17. Removal of Granger as a reference for the reasons already explained is sufficient to overcome the rejection of these claims, and no further comments are needed.

For all of these reasons, applicant respectfully submits that the Granger Patent actually teaches against the invention recited in all the pending claims in the application as amended. Withdrawal of these rejections is requested.

The Vaccine Patent

Claims 1-8, 12-14, and 18-22 stand rejected under 35 USC § 102(a) as being anticipated by PCT publication WO 98/16238. These claims also stand rejected under 35 USC § 102(f), since the WO 98/16238 publication names a different inventive entity. U.S. application 08/948,939, which is the domestic counterpart of WO 98/16238, was issued on March 27, 2001 as U.S. Patent 6,207,147 (the Vaccine Patent).

As explained during the interview, the invention taught and claimed in the Vaccine Patent is a different technology from the implant of alloactivated cells directly into the tumor bed, as taught in the Granger application and the present application.

Accompanying this Amendment is a 37 CFR § 1.132 Declaration by John C. Hiserodt, M.D., who is a named inventor on both the Vaccine Patent and the invention claimed herein. Dr. Hiserodt explains that the Vaccine Patent describes a composition containing *both* alloactivated cells *and tumor antigen*, and is administered at a site *away from the primary tumor.* In contrast, the implant technology of Granger and the present application involves administering alloactivated cells *directly into the tumor bed,* which is a considerably different process, both conceptually and procedurally.

Since the Vaccine Patent relates to a different technology, it neither anticipates nor renders obvious the invention claimed here. Withdrawal of this rejection is respectfully requested.

The Kruse Reference

Claims 1, 2, 6-8, and 21-22 stand rejected under 35 USC § 103(a) as being unpatentable over Kruse et al., (J. Neuro-Oncology, 19:161, 1994). The Office Action points out that the language of the claims as previously presented includes a response *IN* the patient by third-party activator cells that are passively administered, such as the cytotoxic T lymphocytes taught by Kruse.

Applicants thank the Examiner for pointing out this oversight. Claim 1 has now been amended to require that the treatment stimulates a response *BY* the patient against the tumor. In other words, the patient must themselves form a reactive response against the tumor — such as an anti-tumor immunological response (Claim 3), or an anti-tumor inflammatory response (Claim 4). Direct effects on the tumor by the administered cytotoxic lymphocytes of Kruse et al. does not qualify as a response *BY* the host.

Similarly, new claims 23 and its dependents are distinguished from the Kruse reference because the therapy "results in the patient generating a therapeutic response against tumor growth".

Withdrawal of this rejection is respectfully requested.

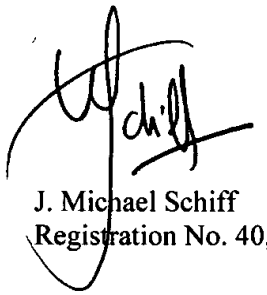
Request for a further Interview

Applicant requests that all outstanding rejections be reconsidered and withdrawn in light of this submission. The application is believed to be in condition for allowance, and prompt issuance of a Notice of Allowance is respectfully requested.

If upon consideration of this paper, the Examiner believes there are further matters to be addressed, applicant hereby requests an interview by telephone.

Should the Patent Office determine that a further extension of time or other relief is required for further consideration of this application, applicant hereby petitions for such relief and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of this document to the Credit Card indicated on accompanying PTO-2038.

Respectfully submitted,



J. Michael Schiff
Registration No. 40,253

808 Coleman Avenue, Suite 19
Menlo Park, CA 94025
Phone: 650-327-0960

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Version with Markings to show

CHANGES MADE

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CANCER IMMUNOTHERAPY USING ALLOSTIMULATED CELLS
IN A MULTIPLE SEQUENTIAL IMPLANTATION STRATEGY

Amended Claims

1. A method for treating cancer in a human patient, comprising:
   a) implanting at or around the site of a tumor in the patient a first cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient such that tumor cells are left at the site; and
   b) implanting at or around the site of a tumor in the patient a second cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient;
   wherein step a) and step b) are separated by an interval of at least three days, whereby the treatment stimulates a response ~~in~~ by the patient against the tumor.

2. The method of claim 1, wherein the first cell population stimulates a response in the patient against the tumor before the implanting of the second cell population.

3. The method of claim 2, wherein the response comprises an inflammatory response.

4. The method of claim 2, wherein the response comprises an immunological response.

5. The method of claim 1, wherein the alloactivated lymphocytes in at least one of the cell populations are alloactivated against leukocytes of the human patient.,

6. The method of claim 1, wherein the alloactivated lymphocytes in at least one of the cell populations are alloactivated against leukocytes of a third-party donor different from the patient or the donor of the lymphocytes.

7. The method of claim 1, wherein the interval is between about one and eight weeks.

8. The method of claim 1, wherein the interval is between about two and twelve months.

9. The method of claim 1, wherein treatment according to the method has at least one of the following effects in at least 30% of treated subjects:
   a) substantial regression of the tumor in size;
   b) lack of recurrence of a tumor after removal; or
   c) decrease in rate of formation of metastasis.

10. The method of claim 1, further comprising removing any residual tumor at or around the site of the second cell population at a time subsequent to when the second cell population was implanted.

11. The method of claim 1, wherein both the first and second cell populations have one or more of the following features:

i) contain between about 2×10^9 and 2×10^{10} cultured peripheral blood mononuclear cells originating from the donor and between about 1×10^8 and 2×10^9 cultured peripheral blood mononuclear cells originating from the patient or from a second donor;

ii) are obtained by a process in which donor lymphocytes are alloactivated by coculturing ex vivo with stimulator leukocytes for a period of about 48 to 72 hours; or

iii) are obtained by a process in which donor lymphocytes are alloactivated by coculturing ex vivo with stimulator leukocytes and harvested at about the time of initial alloactivation, measurable by acridine orange or CD69 assay.

12. ~~A method for treating cancer in a human patient, comprising:~~

~~a) implanting at or around the site of a tumor in the patient a first cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient; and~~

~~b) implanting at or around the site of a tumor in the patient a second cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient;~~

~~wherein step a) and step b) are separated by an interval of at least three days, and~~ The method of claim 1,

wherein the cancer is selected from ~~the group consisting of~~ melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer.

13. ~~A~~ The method of claim 1, which is a-method for eliciting an anti-cancer immune response in a human patient ~~, comprising:~~

~~a) implanting at or around the site of a tumor in the patient a first cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient; and~~

~~b) implanting at or around the site of a tumor in the patient a second cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient;~~

~~wherein step a) and step b) are separated by an interval of at least three days~~.

14. The method of claim 13, wherein the first cell population stimulates ~~a~~ an anti-cancer immune response in the patient ~~against the tumor~~ before the implanting of the second cell population.

~~15. The method of claim 13, wherein treatment according to the method has at least one of the following effects:~~

~~a) substantial regression of the tumor in size;~~

~~b) lack of recurrence of a tumor after removal; or~~

~~c) decrease in rate of formation of metastasis.~~

16. The method of claim ~~13~~ 1, further comprising removing any residual tumor at or around the site of the second cell population at a time subsequent to when the second cell population was implanted.

~~17. The method of claim 13, further comprising the step of removing any residual tumor at or around the site of the implanting of the second cell population at a time subsequent to step c).~~

18. The method of claim ~~13~~ 1, wherein both the first and second cell populations have one or more of the following features:

i) contain between about 2×10^9 and 2×10^{10} cultured peripheral blood mononuclear cells originating from the donor and between about 1×10^8 and 2×10^9

cultured peripheral blood mononuclear cells originating from the patient or from a second donor;

ii) are obtained by a process in which donor lymphocytes are alloactivated by coculturing ex vivo with stimulator leukocytes for a period of about 48 to 72 hours; or

iii) are obtained by a process in which donor lymphocytes are alloactivated by coculturing ex vivo with stimulator leukocytes and harvested at about the time of initial alloactivation, measurable by acridine orange or CD69 assay.

19. A pharmaceutical composition comprising alloactivated lymphocytes allogeneic to leukocytes in a cancer patient packaged with information for the treatment of the patient according to the method of claim 1.

20. A pharmaceutical composition comprising alloactivated lymphocytes allogeneic to leukocytes in a cancer patient packaged with information for the treatment of the patient according to the method of claim ~~13~~ 23.

~~21. The method of claim 1, wherein tumor is not removed from the site at the time of implanting of the first cell population.~~

22. The method of claim ~~23~~ 1, wherein the second cell population is implanted into the same tumor site as the first cell population.

23. An improvement in the method of treating a human patient having a tumor by implanting at or around the site of a solid tumor in the patient a cell population comprising alloactivated lymphocytes that are allogeneic to the patient;

wherein the implanting of the alloactivated lymphocytes results in the patient generating a therapeutic response against tumor growth;

the improvement comprising implanting at or around the site of a solid tumor in the patient a second cell population containing alloactivated lymphocytes that are allogeneic to the patient between 1 and 8 weeks after the implanting of the first cell population.

24. The improved method of claim 23, which elicits an inflammatory response against the tumor.

25. The improved method of claim 23, which elicits an immune response against the tumor.

26. The improved method of claim 23, wherein the alloactivated lymphocytes in at least one of the cell populations are alloactivated against leukocytes of the human patient.,

27. The improved method of claim 23, wherein the alloactivated lymphocytes in at least one of the cell populations are alloactivated against leukocytes of a third-party donor different from the patient or the donor of the lymphocytes.

28. The improved method of claim 23, wherein treatment according to the method has at least one of the following effects in at least 30% of treated subjects:

a) substantial regression of the tumor in size;
b) lack of recurrence of a tumor after removal; or
c) decrease in rate of formation of metastasis.

29. The improved method of claim 23, wherein the tumor is a cancer is selected from melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer.

30. The improved method of claim 23, wherein the first cell population stimulates a response in the patient against the tumor before the implanting of the second cell population.

31. The improved method of claim 23, wherein treatment according to the method has at least one of the following effects:

a) substantial regression of the tumor in size;
b) lack of recurrence of a tumor after removal; or
c) decrease in rate of formation of metastasis.